Syntheses of 10-Oxo, 10α-Hydroxy, and 10β-Hydroxy Derivatives of a Potent κ-Opioid Receptor Agonist, TRK-820

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Syntheses of 10-oxo, 10α-hydroxy, and 10β-hydroxy derivatives of a potent κ-opioid receptor selective agonist, TRK-820, are described. These derivatives were supposed to be potential degradation products in formulation of TRK-820 as a result of autoxidation. 10-Oxo-TRK-820 11 was derived from 10-oxo-4,5-epoxymorphinan 14 in 10 steps in 32% overall yield. Reduction of the 10-oxo group in 4,5-epoxymorphinan with $NaBH_4$ gave 10β-hydroxy-4,5-epoxymorphinan, exclusively. A stepwise inversion method of the 10β-hydroxy group to produce 10α-hydroxy-4,5-epoxymorphinan was established. By HPLC analyses, 10α-hydroxy-TRK-820 12 was confirmed to be one of the degradation products in developing formulation of TRK-820.

Key words TRK-820; degradation product; 10-oxo-4,5-epoxymorphinan; 10-oxo-TRK-820; 10α-hydroxy-TRK-820; 10β-hydroxy-TRK-820

Three types of opioid receptors (μ, δ, κ) are now well established by not only pharmacological studies but also molecular biological studies.[1—3] Especially, the κ-opioid receptor has been of interest because its activation produces analgesia with minimum physical dependence and respiratory depression.[4] Thus, a highly selective κ-opioid agonist may provide a useful analgesic free from abuse potential and the adverse effects of a μ-agonist like morphine.[4,5]

We have already described the design and synthesis of (*E*)-*N*-[17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide monohydrochloride **1**, TRK-820 (Fig. 1), and its pharmacological activity.[6] TRK-820 exhibited high κ-opioid agonistic activity, antipruritic actions,[7,8] and higher analgesic action than morphine and a prototype of κ-opioid agonist, U-50488H.[6] Now clinical trials of TRK-820 are in progress (Phase III in Europe and Phase IIb in Japan) as an antipruritic agent for uraemic pruritus.

Recently, decomposition products of morphine **2**[9] and naltrexone **3**[10] were newly confirmed to occur in formulated samples. The degradation products of morphine **2** were identified to be 10α-hydroxymorphine **4** and 10-oxomorphine **5**, and 2-chloro-10α-hydroxynaltrexone **6** was identified as a degradation product of natrexone **3** (Fig. 2). In a former work, 10-oxomorphine **5** was also identified as a decomposition product in crystalline morphine **2**.[11] TRK-820 has the same 4,5-epoxymorphinan structure like morphine **2** and naltrexone **3**, therefore similar type of degradation products might occur in formulation of TRK-820.

On the other hand, some κ-opioid selective ligands like ketocyclazocine **7**[12] and ethylketocyclazocine **8**[13] have an oxo group in common on their benzylic positions. Furthermore, it was described that introduction of an oxo group at the 10-position of KT-90 **9**,[14] a κ-opioid agonist, gave KT-95 **10**[15] which exhibited higher analgesic activity and affinity to κ-opioid receptor than those of KT-90 (Fig. 3).

Hence we were interested in that similar degradation products, confirmed in morphine **2** and naltrexone **3**, might occur in the developing formulation of TRK-820. In addition to the above assumptions, those oxidative degradation products might have higher selectivity or affinity to κ-opioid receptor as shown in ketocyclazocine **7** and ethylketocyclazocine **8**. To confirm if those compounds actually exist in the developing formulation of TRK-820, we intended to synthesize those oxidative degradation products such as 10-oxo **11**, 10α-hydroxy **12**, and 10β-hydroxy **13** derivatives of TRK-820. Herein we wish to report the syntheses of compounds **11**, **12**, and **13**, starting from 10-oxo-4,5-epoxymorphinan **14** which was prepared by a convenient oxidation method of the 10-benzylic position in 4,5-epoxymorphinan derivatives previously reported by us (Fig. 4).[16] From the synthetic point of view, it was presumed to be difficult to transform the sterically hindered 10β-hydroxy group in 4,5-epoxymorphinan

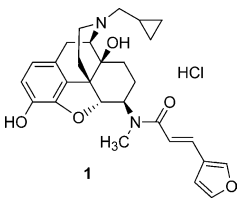

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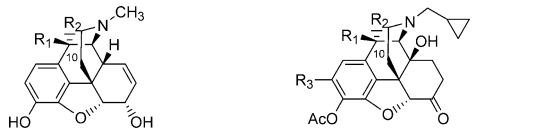
Fig. 1. Structure of TRK-820



2 R_1=H, R_2=H Morphine
4 R_1=H, R_2 = OH 10α-Hydroxymorphine
5 R_1=R_2=O 10-Oxomorphine
3 R_1=H, R_2 = H,R_3=H Naltrexone
6 R_1=H, R_2 =OH,R_3 =Cl
2-Chloro-10α-hydroxynaltrexone

Fig. 2

7 R = CH_3 Ketocyclazocine
8 R = C_2H_5 Ethylketocyclazocine
9 R_1=H, R_2 = H KT-90
10 R_1=R_2=O KT-95

Fig. 3

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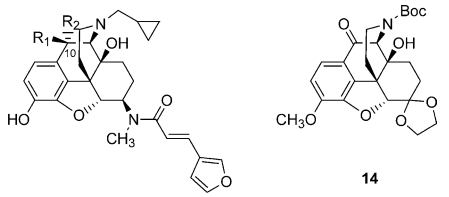


Fig. 4

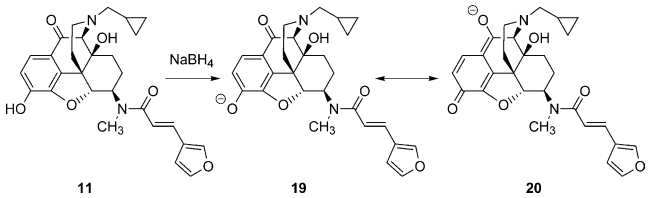


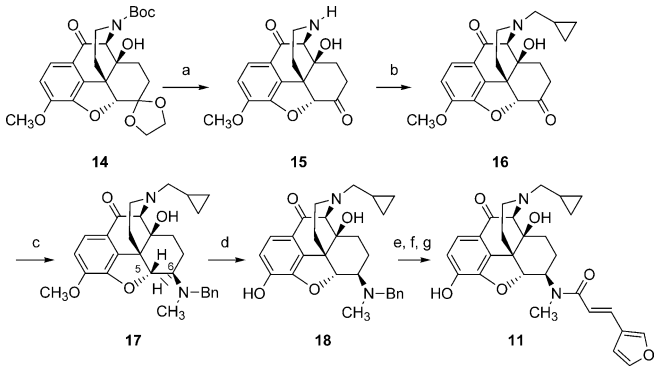
Fig. 5

into the 10α-hydroxy group by inversion reaction. In fact, Mitsunobu reaction[17] was in vain in this system. We also wish to report the effective stepwise inversion method of the 10β-hydroxy group in 4,5-epoxymorphinan.

Results and Discussion

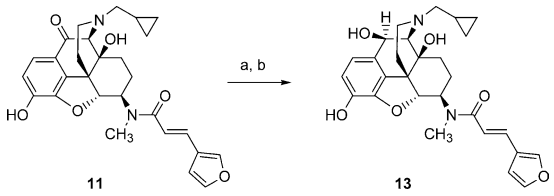
The target compounds were synthesized by a route shown in Charts 1, 2, and 5. 10-Oxo-4,5-epoxymorphinan derivative **14** was used as the starting marterial which was synthesized in accordance with our oxidation method.[16] Deprotection of the Boc and ketal groups of compound **14** under acidic conditions gave diketoamine **15**, and the resulting secondary amino group was alkylated with cyclopropylmethyl bromide in the presence of potassium iodide and potassium carbonate to afford diketone **16** in 79% yield (2 steps). Stereoselective reductive-amination of compound **16** with *N*-benzylmethylamine by using $NaBH_3CN$ was performed in accordance with the literature[18] to give compound **17** in 66% yield after chromatographic separation. The reaction proceeded regioselectively only on the 6-oxo group due to the steric bulkiness on the 10-oxo group. The stereochemistry of the 6-position was elucidated to be 6β configuration by ^{1}H-NMR spectral analysis of the 5-proton, which was observed at δ=4.80 with an axial–axial coupling of 8.1 Hz between the 5- and 6-protons. Demethylation of compound **17** by using thiolate anion produced phenol **18** in 91% yield. Phenol **18** was debenzylated by hydrogenolysis and the resulting crude product which has a secondary amino group and a 3-hydroxy group was reacted with 2 equivalents of (*E*)-3-(3-furyl)acryloyl chloride in the presence of sodium carbonate to produce amide ester intermediate. This phenol ester portion was hydrolyzed by addition of 2.5 M NaOH solution to produce 10-oxo-TRK-820 **11** in 81% yield (3 steps).

With compound **11** in hand, the next step was to synthesize 10α-hydroxy compound **12** and its 10β-epimer **13** by hydride reduction of the 10-oxo group in compound **11**. Treatment of compound **11** with $NaBH_4$ in CH_3OH resulted in complete recovery of the starting material **11**. The results suggest that compound **11** is easily convertible into quinonmethide form **20** under the hydride reduction conditions (Fig. 5).



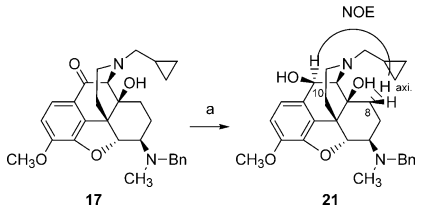
Reagents and conditions: (a) 3 M HCl, 1,4-dioxane, reflux, 21 h; (b) KI, K_2CO_3, cyclopropylmethyl bromide, dry DMF, room temperature, 3.5 h (79% in 2 steps); (c) $BnNHCH_3$, $PhCO_2H$, PhH, reflux, 16 h; $NaBH_3CN$, CH_3OH, 0 °C to room temperature, 1.5 h (66%); (d) *n*-PrSH, NaH, dry DMF, 95 °C, 3 h (91%); (e) H_2, 10% Pd–C, *o*-phthalic acid, CH_3OH, $CHCl_3$, room temperature, 12.5 h; (f) (*E*)-3-(3-furyl)acryloyl chloride, Na_2CO_3, THF, H_2O, room temperature, 1.5 h; (g) 2.5 M NaOH, CH_3OH, room temperature, 1 h (81% in 3 steps).

Chart 1



Reagents and conditions: (a) Ac_2O, $NaHCO_3$, H_2O, 1,4-dioxane, room temperature, 16.5 h (81%); (b) $NaBH_4$, CH_3OH, 0 °C to room temperature, 2.5 h (71%).

Chaer 2



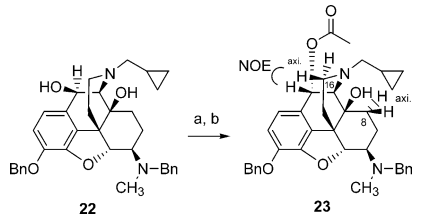
Reagents and conditions: (a) $NaBH_4$, CH_3OH, 0 °C to room temperature, 22 h (60%).

Chart 3

Thus, the 3-hydroxy group of compound **11** was acetylated and the resulting acetate was treated with $NaBH_4$ in CH_3OH at room temperature to successfully give 10β-hydroxy-TRK-820 **13** exclusively. In this reaction, both the reduction of 10-oxo group and the deacetylation were taken place (Chart 2).

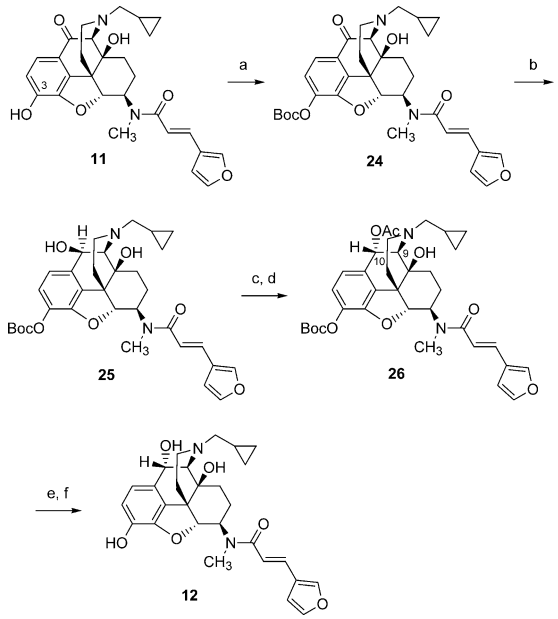
The stereochemistry of the 10-position on compound **13** was elucidated to be 10β-hydroxy configuration by ^{1}H-NMR spectral analysis of the 10-proton, which was observed at δ=5.03 (1H, d, J=5.1 Hz) that was similar to the literatures.[10,12]

A similar stereoselectivity of 10-oxo hydride reduction was observed by reduction of model compound **17** (Chart 3). Stereochemistry of the resulting compound **21** was analyzed by NOESY and COSY spectra, and positive NOE signal was observed between the 8-axial proton and the 10-position proton. The results and the reported fact[19] that $NaBH_4$ reduction of 10-oxomorphinan derivatives gave 10β-hydroxy compounds allowed the stereochemistry of the 10-position in compounds **13** and **21** to be identified as 10β-hydroxy configuration.



Reagents and conditions: (a) MsCl, Et_3N, dry CH_2Cl_2, 0 °C, 2 h; (b) NaOAc, AcOH, 0 °C to room temperature, 18 h (71% in 2 steps).

Chart 4



Reagents and conditions: (a) $(Boc)_2O$, Na_2CO_3, *n*-Bu_4NI, H_2O, $CHCl_3$, room temperature, 54.5 h (quant.); (b) $NaBH_4$, CH_3OH, 0—5 °C, 2 h (quant.); (c) MsCl, Et_3N, dry CH_2Cl_2, 0 °C to room temperature, 20 h; (d) NaOAc, AcOH, room temperature, 10.5 h (69% in 2 steps); (e) aq. NaOH, THF, room temperature, 48 h; (f) 28% ammonia solution, CH_3OH, room temperature, 43 h (81% in 2 steps).

Chart 5

Then we tried inversion of the 10β-hydroxy group to synthesize the 10α-hydroxy compound by using model compound **22** (Chart 4). Although the inversion did not proceed under Mitsunobu's conditions,[17] stepwise treatments of compound **22** with methanesulfonyl chloride in the presence of triethylamine followed by sodium acetate in acetic acid successfully gave 10α-acetate **23** in 71% yield (2 steps) exclusively. The stereochemistry of the 10-position in 10α-acetate **23** was also elucidated by NOESY and COSY spectra. Positive NOE signal was observed between the 16-axial proton and the 10-position proton.

Next, we applied the above stepwise inversion method to the synthesis of 10α-hydroxy-TRK-820 **12** (Chart 5). The 3-hydroxy group of 10-oxo-TRK-820 **11** was protected by the Boc group[20] which is more stable than an acetyl group under basic conditions. The 10-Oxo group of compound **24** was reduced by $NaBH_4$ in CH_3OH to give 10β-hydroxy-3-*O*-Boc compound **25** in quantitative yield, which was subjected to the above stepwise inversion sequence to produce 10α-acetoxy-3-*O*-Boc compound **26** in 69% yield (2 steps). The stereochemistry of the 10-position on compound **26** was elucidated to be 10α configuration by ^{1}H-NMR analysis of the 10-proton, which was observed at δ=6.23 (1H, s). No coupling constant ($J_{9—10}$=0 Hz) of the 10-proton strongly suggests the 10β-H configuration.[10] The 3-*O*-Boc group and the 10α-acetoxy group were successively hydrolyzed by aqueous sodium hydroxide, then ammonium hydroxide to finally produce 10α-hydroxy-TRK-820 **12**.

Compounds **11**, **12**, and **13** were measured on HPLC analyses[21] with developing formulation of TRK-820. Retention time of one decomposition product (relative retention time 0.8 *versus* TRK-820 in HPLC analyses) in the developing formulation of TRK-820 was coincident with that of compound **12**. Its coincidence was subsequently confirmed by HPLC spiking experiments using compound **12**. The results indicated that compound **12** was actually identified to be one of the oxidative degradation products in formulated samples of TRK-820. The degradation pattern of TRK-820 in the developing formulation was considered to be similar to those of morphine **2** and naltrexone **3**.

Conclusion

Three types of the 10-position oxidized derivatives of TRK-820 (10-oxo-TRK-820 **11**, 10α-hydroxy-TRK-820 **12**, and 10β-hydroxy-TRK-820 **13**) were synthesized from 10-oxo-4,5-epoxymorphinan **14** which was easily derived from noroxycodone. The overall yields of the above derivatives were 32% in 7 steps (10-oxo-TRK-820), 18% in 9 steps (10β-hydroxy-TRK-820), and 18% in 13 steps (10α-hydroxy-TRK-820), respectively. In this study, the stepwise inversion method of the 10β-hydroxy group in 4,5-epoxymorphinan system was established. Compound **12** was confirmed to be one of the degradation products in the developing formulation of TRK-820 by HPLC analyses. Detailed formulation studies for control of the degradation products and pharmacological studies of compounds **11**, **12**, and **13** are now under way.

Experimental

General Methods All reactions requiring anhydrous conditions were conducted under atmosphere of dry argon. Syntheses of compounds **11**, **12**, **13**, **24**, **25**, and **26** were carried out under protection from light. The progress of reactions and purity of intermediates were monitored on Merck analytical silica gel TLC plates 60 F_{254}. For column chromatography Merck silica gel 60 (0.063—0.200 mm) was used. Melting points were measured on Yanaco MP-500D melting point apparatus without correction. ^{1}H-NMR spectra were measured (TMS internal standard) on Varian Gemini 2000 (300 MHz) or unityplus (500 MHz) spectrometer. IR spectra were measured on JASCO FT/IR-410. Electron ionization mass spectra (EI-MS) and high-resolution electron ionization mass spectra (HR-EI-MS) were measured on JMS-DX303. Electrospray ionization mass spectra (ESI-MS) and high-resolution electrospray mass spectra (HR-ESI-MS) were measured on micromass LCT. LC-MS were measured on Waters micromass ZQ.

4,5α-Epoxy-14β-hydroxy-3-methoxymorphinan-6,10-dione (15) To a stirred solution of compound **14** (74.45 g, 162.0 mmol) in 600 ml of 1,4-dioxane was added a 3 M aq. HCl solution (400 ml, 1200 mmol), and the mixture was heated under reflux for 21 h. The solution was concentrated and then cooled to 0 °C. The mixture was basified by adding a 3.9 M aq. NaOH solution (300 ml, 1175 mmol) and saturated aq. $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$, and the organic layer was concentrated *in vacuo* to give 44.76 g of compound **15** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58—1.73 (2H, m), 1.93—2.00 (1H, m), 2.34 (1H, dt, *J*=14.4, 3.0 Hz), 2.50—2.70 (2H, m), 2.78—2.85 (1H, m), 3.06 (1H, dt, *J*=14.7, 5.4 Hz), 3.25 (1H, s), 4.02 (3H, s), 4.75 (1H, s), 4.85 (1H, broad s), 6.89 (1H, d, *J*=8.4 Hz), 7.47 (1H, d, *J*=8.4 Hz). IR (KBr) cm^{-1}: 3356, 1723, 1681, 1598, 1497, 1281. HR-EI-MS *m/z* M^+ Calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1093.

17-(Cyclopropylmethyl)-4,5α-epoxy-14β-hydroxy-3-methoxymorphi-

nan-6,10-dione (16) To a stirred suspension of compound **15** (44.50 g, 141 mmol), KI (47.33 g, 285 mmol), and K_2CO_3 (40.39 g, 292 mmol) in 700 ml of dry DMF was added dropwise cyclopropylmethy bromide (27.5 ml, 283 mmol) at room temperature. After stirring for 3.5 h, water was added to the suspension and extracted with $CHCl_3$. The organic layer was concentrated, and water was added to the residue. The mixture was extracted with EtOAc, and the organic layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give 44.77 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (20/1) gave 41.14 g (79%) of compound **16** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.10—0.16 (1H, m), 0.33—0.38 (1H, m), 0.52—0.60 (2H, m), 0.94 (1H, m), 1.63 (1H, dt, J=13.9, 4.2 Hz), 1.74 (1H, dt, J=13.0, 3.0 Hz), 1.93—2.01 (1H, m), 2.18 (1H, dt, J=12.4, 4.2 Hz), 2.24—2.38 (2H, m), 2.56—2.72 (2H, m), 2.90 (1H, dd, J=12.7, 5.7 Hz), 3.06 (1H, dt, J=14.4, 5.1 Hz), 3.32 (1H, s), 4.01 (3H, s), 4.77 (1H, s), 4.98 (1H, s), 6.86 (1H, d, J=8.4 Hz), 7.42 (1H, d, J=8.4 Hz). IR (KBr) cm^{-1}: 3447, 1727, 1671, 1594, 1502, 1271. HR-EI-MS m/z M^+ Calcd for $C_{21}H_{23}NO_5$: 369.1576. Found: 369.1602.

6β-(*N*-Benzyl)methylamino-17-(cyclopropylmethyl)-4,5α-epoxy-14β-hydroxy-3-methoxymorphinan-10-one (17) A stirred mixture of compound **16** (41.11 g, 111.2 mmol), *N*-benzylmethylamine (29.0 ml, 224.7 mmol), and benzoic acid (13.76 g, 112.6 mmol) in 700 ml of benzene was refluxed for 16 h using a Dean–Stark apparatus. After removing benzene, the mixture was dissolved in 1000 ml of CH_3OH. To the stirred mixture was added $NaBH_3CN$ (14.03 g, 223.0 mmol) at 0 °C. After stirring for 10 min, the temperature was raised to room temperature and the stirring was continued for 1.5 h. After that, the solution was concentrated and the residue was dissolved in $CHCl_3$ and a saturated aq. $NaHCO_3$ solution. The organic layer was separated, and dried over Na_2SO_4, and concentrated *in vacuo* to give 83.11 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (50/1) gave 34.78 g (66%) of compound **17** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.06—0.12 (1H, m), 0.28—0.33 (1H, m), 0.48—0.56 (2H, m), 0.92 (1H, m), 1.32 (1H, dt, J=13.8, 2.4 Hz), 1.52—1.71 (3H, m), 1.97—2.23 (3H, m), 2.36 (3H, s), 2.39 (1H, dt, J=12.7, 5.4 Hz), 2.54—2.67 (2H, m), 2.82 (1H, dd, J=12.1, 5.1 Hz), 3.20 (1H, s), 3.66 (1H, d, J=13.5 Hz), 3.81 (1H, d, J=13.5 Hz), 3.97 (3H, s), 4.80 (1H, d, J=8.1 Hz), 6.82 (1H, d, J=8.4 Hz), 7.17—7.35 (4H, m), 7.35—7.39 (2H, m). IR (KBr) cm^{-1}: 3433, 1672, 1618, 1507, 1286. HR-EI-MS m/z M^+ Calcd for $C_{29}H_{34}N_2O_4$: 474.2519. Found: 474.2516.

6β-(*N*-Benzyl)methylamino-17-(cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxymorphinan-10-one (18) To a stirred suspension of sodium hydride (1.81 g, 45.2 mmol) in 60 ml of dry DMF was added dropwise *n*-PrSH (4.10 ml, 45.2 mmol) in an ice cooled bath, and the mixture was stirred for 90 min. To the stirred suspension was added dropwise a solution of compound **17** (5.25 g, 11.06 mmol) in 65 ml of dry DMF, and the mixture was heated at 95 °C for 3 h. Water was slowly added to the suspension and then solid NaCl was added. The mixture was extracted with $CHCl_3$, and the organic layer was concentrated *in vacuo* to give 7.18 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (50/1) gave 4.64 g (91%) of compound **18** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.07—0.12 (1H, m), 0.28—0.33 (1H, m), 0.48—0.56 (2H, m), 0.88—0.94 (1H, m), 1.23—1.32 (1H, m), 1.60—2.00 (4H, m), 2.10—2.30 (2H, m), 2.33 (3H, s), 2.30—2.41 (1H, m), 2.45—2.55 (1H, m), 2.63 (1H, dd, J=13.0, 6.0 Hz), 2.70—2.86 (1H, dd, J=12.1, 4.5 Hz), 3.20 (1H, s), 3.45 (1H, d, J=13.5 Hz), 3.84 (1H, d, J=13.5 Hz), 4.73 (1H, d, J=8.4 Hz), 6.82 (1H, d, J=8.4 Hz), 7.20—7.33 (6H, m). IR (KBr) cm^{-1}: 3422, 1669, 1613, 1292. HR-EI-MS m/z M^+ Calcd for $C_{28}H_{32}N_2O_4$: 460.2362. Found: 460.2336.

(*E*)-*N*-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxy-10-oxomorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (11) To a solution of compound **18** (31.48 g, 68.35 mmol) in 120 ml of $CHCl_3$ and 500 ml of CH_3OH was added *o*-phthalic acid (11.76 g, 70.78 mmol) and 10% Pd–C (20.12 g), and the mixture was stirred under a hydrogen atmosphere at room temperature for 12.5 h. The Pd–C catalyst was then removed by filtration through hyflo super-cell® and washed with CH_3OH. The CH_3OH solution was concentrated *in vacuo* to give 44.76 g of secondary amine,[21] which was used in the next steps without further purification. To a stirred solution of the above crude products (42.86 g, 68.35 mmol) in 300 ml of water and 300 ml of THF was added Na_2CO_3 (24.33 g, 204.7 mmol) followed by (*E*)-3-(3-furyl)acryloyl chloride (21.78 g, 139 mmol) at room temperature. After stirring for 1.5 h, the reaction mixture was quenched with conc. HCl for neutralization in an ice bath, and then a saturated aq. $NaHCO_3$ solution was added to basify. The resultant mixture was extracted with EtOAc, and the combined organic layer was concentrated *in vacuo* to give 38.97 g of crude products. To a stirred solution of the crude products in 320 ml of CH_3OH was added a 2.5 M aq. NaOH solution (45.0 ml, 112 mmol), and stirring was continued at room temperature for 1 h. After the reaction was completed, 3 M aq. HCl solution was added dropwise to the solution for neutralization in an ice bath, and saturated aq. $NaHCO_3$ solution was added to basify. Then CH_3OH was removed by concentration, and the resulting residue was extracted with $CHCl_3$. The organic layer was concentrated *in vacuo* to give 46.36 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (100/1—50/1) gave 33.22 g of the residue, and this residue was precipitated by EtOAc/CH_3OH (3/1) to give 21.21 g of compound **11**. The filtrate was repeatedly purified to give totally 27.08 g (81% in 3 steps) of compound **11** as a pale yellow powder.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.07—0.20 (1H, m), 0.30—0.40 (1H, m), 0.50—0.60 (2H, m), 0.90—1.00 (1H, m), 1.40—2.00 (3H, m), 2.10—2.30 (4H, m), 2.30—2.50 (1H, m), 2.66 (1H, dd, J=12.9, 6.3 Hz), 2.80—2.90 (1H, m), 3.06 (2H, s), 3.15 (1H, s), 3.23—3.27 (1H, m), 3.70—3.80 (0.7H, m), 4.58—4.64 (2H, m), 4.64—4.80 (0.3H, m), 6.26 (0.7H, d, J=15.6 Hz), 6.56—6.63 (1.3H, m), 6.90 (0.3H, d, J=8.4 Hz), 7.01 (0.7H, d, J=8.4 Hz), 7.20—7.45 (3.4H, m), 7.59 (0.3H, d, J=15.6 Hz), 7.64 (0.3H, s). IR (KBr) cm^{-1}: 3411, 1650, 1616, 1292. HR-EI-MS m/z M^+ Calcd for $C_{28}H_{30}N_2O_6$: 490.2104. Found: 490.2084. mp 198 °C (dec.).

(*E*)-*N*-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,10β,14β-trihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (13) To a stirred solution of compound **11** (2.03 g, 4.13 mmol) in 45 ml of 1,4-dioxane was added $NaHCO_3$ (3.71 g, 44.1 mmol) in 15 ml of water followed by Ac_2O (2.00 ml, 21.2 mmol) at room temperature. After stirring for 16.5 h, the reaction mixture was extracted with EtOAc, and the organic layer was washed with water and a saturated aq. NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to give 2.09 g of crude products. This was chromatographed on silica gel. Elution with *n*-hexane/EtOAc (1/2) gave 1.79 g (81%) of 3-*O*-acetate. To a stirred solution of the product (1.78 g, 3.34 mmol) in 30 ml of CH_3OH was added $NaBH_4$ (300.0 mg, 7.93 mmol) at room temperature. After stirring for 2.5 h, a saturated aq. $NaHCO_3$ solution was added to the reaction mixture, and the mixture was extracted with $CHCl_3$. The organic layer was washed with a saturated aq. NaCl solution, and dried over Na_2SO_4, and concentrated *in vacuo* to give 1.62 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (30/1—10/1) gave 1.17 g (71%) of compound **13** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.15—0.20 (2H, m), 0.48—0.57 (2H, m), 0.82—0.95 (1H, m), 1.37—1.47 (3H, m), 1.60—1.75 (1H, m), 2.10—2.30 (2H, m), 2.59—2.66 (1H, m), 2.76—2.89 (2H, m), 2.96—3.04 (1H, m), 3.00 (2H, s), 3.13 (1H, s), 3.15—3.18 (1H, m), 3.65—3.80 (0.7H, m), 4.48 (0.7H, d, J=8.1 Hz), 4.49—4.62 (0.6H, m), 5.03 (1H, d, J=5.1 Hz), 6.33 (0.7H, d, J=15.3 Hz), 6.56 (0.3H, d, J=15.3 Hz), 6.59 (0.3H, d, J=1.7 Hz), 6.66 (0.7H, d, J=1.7 Hz), 6.85 (0.3H, d, J=8.2 Hz), 6.90 (0.3H, d, J=8.2 Hz), 6.94 (1.4H, broad s), 7.32 (0.7H, d, J=1.7 Hz), 7.38 (0.3H, d, J=1.7 Hz), 7.39 (0.7H, s), 7.40 (0.7H, d, J=15.3 Hz), 7.54 (0.3H, d, J=15.3 Hz), 7.62 (0.3H, s). IR (KBr) cm^{-1}: 3391, 1647, 1593. HR-EI-MS m/z M^+ Calcd for $C_{28}H_{32}N_2O_6$: 492.2260. Found: 492.2284.

6β-(*N*-Benzyl)methylamino-17-(cyclopropylmethyl)-4,5α-epoxy-10β,14β-dihydroxy-3-methoxymorphinan (21) To a stirred solution of compound **17** (231 mg, 0.486 mmol) in 10 ml of CH_3OH was added $NaBH_4$ (82.0 mg, 2.16 mmol) at room temperature. After stirring for 23 h, a saturated aq. $NaHCO_3$ solution was added to the reaction mixture, and extracted with $CHCl_3$. The organic layer was washed with saturated aq. NaCl solution, and dried over Na_2SO_4, and concentrated *in vacuo* to give 224 mg of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (50/1—20/1) gave 140 mg (60%) of compound **21** as an amorphous solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.11—0.19 (2H, m), 0.46—0.55 (2H, m), 0.86—0.94 (1H, m), 1.30 (1H, dt, J=12.5, 3.5 Hz), 1.40 (1H, dd, J=13.0, 2.5 Hz), 1.51—1.55 (1H, m), 1.62 (1H, dt, J=13.5, 3.7 Hz), 1.91—2.00 (1H, m), 2.27 (1H, dt, J=12.5, 5.0 Hz), 2.33 (3H, s), 2.54—2.63 (2H, m), 2.77—2.86 (2H, m), 3.00 (1H, dd, J=13.2, 6.2 Hz), 3.13 (1H, d, J=5.3 Hz), 3.71 (1H, d, J=13.5 Hz), 3.78 (1H, d, J=13.5 Hz), 3.90 (3H, s), 4.73 (1H, d, J=7.0 Hz), 4.96 (1H, d, J=5.3 Hz), 6.79 (1H, d, J=8.3 Hz), 6.90 (1H, d, J=8.3 Hz), 7.20 (1H, t, J=7.5 Hz), 7.28 (2H, t, J=7.5 Hz), 7.36 (2H, d, J=7.5 Hz).

10α-Acetoxy-6β-(*N*-benzyl)methylamino-3-benzyloxy-17-(cyclopropylmethyl)-4,5α-epoxy-14β-hydroxymorphinan (23) To a stirred solution of compound **22** (295 mg, 0.533 mmol) in dry CH_2Cl_2 was added dropwise Et_3N (0.450 ml, 3.22 mmol) followed by MsCl (0.08 ml, 1.03 mmol) at 0 °C.

After stirring for 2 h, to this solution was added dropwise a solution of NaOAc (612 mg, 7.46 mmol) in 8.0 ml of acetic acid at 0 °C and the temperature was gradually raised to room temperature. After stirring for 18 h, this solution was poured into saturated aq. $NaHCO_3$ solution to basify and the mixture was extracted with $CHCl_3$. The organic layer was washed with a saturated aq. NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to give 332 mg of crude products. This was chromatographed on silica gel. Elution with *n*-hexane/EtOAc (2/1—1/1—0/1) gave 226 mg (71%) of compound **23** as an amorphous solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.13—0.16 (2H, m), 0.50—0.55 (2H, m), 0.86—0.90 (1H, m), 1.50 (1H, dd, J=13.0, 2.5 Hz), 1.60—1.64 (2H, m), 1.68—1.74 (1H, m), 1.88—2.03 (1H, m), 2.04—2.10 (1H, m), 2.06 (3H, s), 2.23 (1H, dt, J=12.5, 5.3 Hz), 2.34 (3H, s), 2.43 (1H, dd, J=12.5, 6.9 Hz), 2.64—2.72 (3H, m), 2.94 (1H, s), 3.72 (1H, d, J=13.8 Hz), 3.81 (1H, d, J=13.8 Hz), 4.77 (1H, d, J=7.9 Hz), 4.82 (1H, broad s), 5.23 (2H, s), 6.17 (1H, s), 6.74 (1H, d, J=8.3 Hz), 6.82 (1H, d, J=8.3 Hz), 7.17—7.21 (1H, m), 7.23—7.31 (3H, m), 7.34 (2H, t, J=7.3 Hz), 7.38 (2H, d, J=7.3 Hz), 7.44 (2H, d, J=7.3 Hz).

(*E*)-*N*-[3-*tert*-Butoxycarbonyloxy-17-(cyclopropylmethyl)-4,5α-epoxy-14β-hydroxy-10-oxomorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (24) To a stirred solution of compound **11** (26.91 g, 54.85 mmol) in 500 ml of $CHCl_3$ was added Na_2CO_3 (36.74 g, 346.6 mmol), 300 ml of water, $(Boc)_2O$ (30.0 ml, 130.5 mmol), and *n*-Bu_4NI (4.92 g, 13.31 mmol) successively at room temperature. After stirring for 54.5 h, to the reaction mixture was added solid NaCl, and the mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give 71.61 g of crude products. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (50/1) gave 36.43 g (quant.) of compound **24** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.02—0.10 (1H, m), 0.20—0.30 (1H, m), 0.40—0.50 (2H, m), 0.70—0.90 (1H, m), 1.34 (7H, s), 1.35—1.45 (1H, m), 1.43 (2H, s), 1.45—1.70 (3H, m), 2.00—2.30 (2.6H, m), 2.30—2.50 (1.4H, m), 2.53 (1H, dd, J=13.0, 6.0 Hz), 2.90—3.05 (1H, m), 2.93 (2H, s), 3.06 (1H, s), 3.21 (1H, s), 3.55—3.70 (0.7H, m), 3.70—3.85 (0.3H, m), 4.73 (1.6H, d, J=7.5 Hz), 5.08 (0.4H, d, J=7.5 Hz), 6.37 (0.6H, d, J=15.0 Hz), 6.45—6.55 (1.4H, m), 7.03—7.10 (1H, m), 7.28—7.45 (3H, m), 7.51 (1H, s). IR (KBr) cm^{-1}: 3423, 1764, 1682, 1654, 1611, 1276, 1241, 1143. HR-EI-MS m/z M^+ Calcd for $C_{33}H_{38}N_2O_8$: 590.2628. Found: 590.2612.

(*E*)-*N*-[3-*tert*-Butoxycarbonyloxy-17-(cyclopropylmethyl)-4,5α-epoxy-10β,14β-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (25) To a stirred solution of compound **24** (36.31 g, 54.85 mmol) in 300 ml of CH_3OH was added $NaBH_4$ (5.22 g, 137.9 mmol) at 0—5 °C. After stirring for 2 h, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and water. The organic layer was partitioned and washed with a saturated aq. $NaHCO_3$ solution and saturated aq. NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to give 40.08 g of crude products. The residue was treated with THF to give precipitate of compound **25** (26.96 g, 82%) and 8.69 g of the residue from the filtrate. This was chromatographed on silica gel. Elution with $CHCl_3$/CH_3OH (50/1—25/1) gave 5.87 g (18%) of compound **25**. Totally 32.83 g (quant.) of compound **25** was obtained as a white powder.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.15—0.30 (2H, m), 0.50—0.70 (2H, m), 0.90—1.10 (1H, m), 1.43 (7H, s), 1.51 (2H, s), 1.30—1.60 (1H, m), 1.60—1.80 (3H, m), 2.20—2.50 (3H, m), 2.50—2.80 (2H, m), 2.80—2.90 (1H, m), 3.00 (3H, s), 3.18 (1H, s), 3.50—3.65 (0.3H, m), 3.65—3.80 (0.7H, m), 4.71 (0.7H, d, J=7.5 Hz), 4.95—5.15 (1.3H, m), 6.40—6.60 (1.4H, m), 6.70 (0.6H, s), 7.00—7.10 (2H, m), 7.40 (1.4H, d, J=16.2 Hz), 7.47—7.57 (0.6H, m), 7.60—7.65 (1H, m). IR (KBr) cm^{-1}: 3402, 1761, 1651, 1599, 1278, 1246, 1145. HR-ESI-MS m/z $[M+H]^+$ Calcd for $C_{33}H_{41}N_2O_8$: 593.2863. Found: 593.2870. mp 169 °C.

(*E*)-*N*-[10α-Acetoxy-3-*tert*-butoxycarbonyloxy-17-(cyclopropylmethyl)-4,5α-epoxy-14β-hydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (26) To a stirred solution of compound **25** (32.08 g, 54.12 mmol) in 500 ml of CH_2Cl_2 was added dropwise Et_3N (70.0 ml, 502 mmol) followed by MsCl (12.60 ml, 162 mmol) at 0 °C, and the temperature was gradually raised to room temperature. After stirring for 20 h, a saturated aq. $NaHCO_3$ solution was added to the solution, and the mixture was extracted with $CHCl_3$. The organic layer was washed with a saturated aq. NaCl solution, and dried over Na_2SO_4, and concentrated *in vacuo* to give 46.13 g of crude products. To a stirred solution of the crude products in 400 ml of $CHCl_3$ was added a solution of NaOAc (16.75 g, 204.1 mmol) in 175 ml of acetic acid at room temperature. After stirring for 10.5 h, this solution was poured into 28% ammonia solution to basify and the mixture was extracted with $CHCl_3$. The organic layer was washed with a saturated aq. NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to give 40.77 g of crude products. This was chromatographed on silica gel. Elution with *n*-hexane/EtOAc gave 23.84 g (69% in 2 steps) of compound **26** as an amorphous solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.08—0.21 (2H, m), 0.45—0.60 (2H, m), 0.75—0.95 (1H, m), 1.43 (7H, s), 1.51 (2H, s), 1.30—1.60 (1H, m), 1.60—1.70 (3H, m), 1.70—1.90 (1H, m), 2.09 (3H, s), 2.20—2.40 (2H, m), 2.40—2.60 (1H, m), 2.60—2.80 (2H, m), 3.02 (3H, s), 3.14 (1H, s), 3.65—3.80 (0.7H, m), 3.80—4.00 (0.3H, m), 4.75 (0.8H, d, J=7.8 Hz), 5.08 (0.2H, d, J=8.4 Hz), 6.23 (1H, s), 6.53 (1H, d, J=15.3 Hz), 6.60 (0.3H, s), 6.73 (0.7H, s), 6.80—6.90 (0.3H, m), 6.90 (0.7H, d, J=8.4 Hz), 7.01 (0.3H, d, J=8.7 Hz), 7.08 (0.7H, d, J=8.7 Hz), 7.39 (1H, s), 7.48 (1H, d, J=15.3 Hz), 7.62 (1H, s). IR (KBr) cm^{-1}: 3418, 1763, 1739, 1654, 1612, 1277, 1232, 1144. HR-ESI-MS m/z $[M+H]^+$ Calcd for $C_{35}H_{43}N_2O_9$: 635.2969. Found: 635.3000.

(*E*)-*N*-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,10α,14β-trihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide (12) To a stirred solution of compound **2**6 (23.80 g, 37.49 mmol) in 300 ml of THF was added dropwise a solution of NaOH (3.01 g, 75.25 mmol) in 150 ml of water at room temperature. After stirring for 3 h, 150 ml of water was added to the mixture and stirring was continued for 45 h for hydrolysis of the acetate portion. The reaction mixture was extracted with EtOAc, washed with a saturated aq. NaCl solution, and concentrated *in vacuo* to give 22.77 g of crude products. To a stirred solution of the crude products (22.77 g, 37.49 mmol) in 250 ml of CH_3OH was added 70 ml of 28% ammonia solution at room temperature. After stirring for 43 h, a white solid was precipitated. The resultant solid was filtered and washed with CH_3OH, dried under vacuum conditions to give 13.03 g of compound **12**. The above filtrate was purified repeatedly to give 1.92 g of compound **12**. Totally 14.95 g (81% in 2 steps) of compound **12** was obtained as a white powder.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.05—0.26 (2H, m), 0.40—0.60 (2H, m), 0.85—1.00 (1H, m), 1.15—1.40 (2H, m), 1.40—1.50 (1H, m), 1.75—1.85 (1H, m), 1.85—2.00 (1H, m), 2.00—2.25 (2H, m), 2.30—2.40 (1H, m), 2.40—2.60 (2H, m), 2.84 (2H, s), 2.92 (1H, s), 3.08 (1H, s), 3.50—3.65 (0.7H, m), 4.15—4.25 (0.3H, m), 4.63 (0.7H, d, J=8.1 Hz), 4.65—4.90 (1.3H, m), 5.20 (0.4H, d, J=4.5 Hz), 5.25 (0.6H, d, J=5.1 Hz), 6.41 (0.6H, d, J=15.3 Hz), 6.65 (0.8H, s), 6.70—6.85 (2H, m), 6.89 (0.4H, d, J=15.3 Hz), 7.00 (0.2H, s), 7.21 (0.7H, d, J=15.3 Hz), 7.36 (0.3H, d, J=15.3 Hz), 7.67 (0.7H, s), 7.71 (0.3H, s), 7.92 (0.6H, s), 8.02 (0.4H, s), 9.18 (0.3H, broad s), 9.63 (0.6H, broad s). IR (KBr) cm^{-1}: 3378, 3218, 1645, 1594, 1504, 1442, 1403, 1318, 1159. HR-EI-MS m/z M^+ Calcd for $C_{28}H_{32}N_2O_6$: 492.2260. Found: 492.2279. mp 262 °C (dec.).

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21) The samples were measured on a Shimadzu LC-10A series (UV at 280 nm) with an analytical column (YMC-Pack AM-303, 250× 4.6 mm; YMC). The HPLC conditions were as follows: mobile phase, 50 mM NaH_2PO_4 aq. solution/CH_3CN=95/5 (V/V) (A) and 50 mM NaH_2PO_4 aq. solution/CH_3CN=60/40 (V/V) (B); flow rate, 1.0 ml/min; column temperature, 40 °C. The gradient elution profile was 0 to 0% B for 0 to 10 min, 0 to 100% B for 10 to 75 min.
22) The crude products showed no signals for *N*-benzylic protons of compound **18** in ^{1}H-NMR spectral analysis and molecular ion peak (m/z=371 $[M+H]^+$) corresponding to the desired secondary amine in LC-MS analysis.